

COMPOSITIONS FOR NASAL ADMINISTRATION OF DESMOPRESSIN

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Abstract

An aqueous composition for spray nasal administration of a synthetic analog of vasopressin (desmopressin; 1-deamino-8-D-arginine-vasopressin) contains between 2.5 and 7.5 μ g per 100 μ l. The composition may additionally contain an osmotic-pressure controlling agent, such as sodium chloride, a preservative, such as chlorobutanol or benzalkonium chloride, and a buffer stabilizing the pH between about 4 and 6. Buffers containing citrate and/or phosphate are preferred. Also disclosed is a sealed container filled with the composition, an assembly comprising the container and a spray pump, and the use of the composition, the container, and the assembly in the management of urinary disorders.

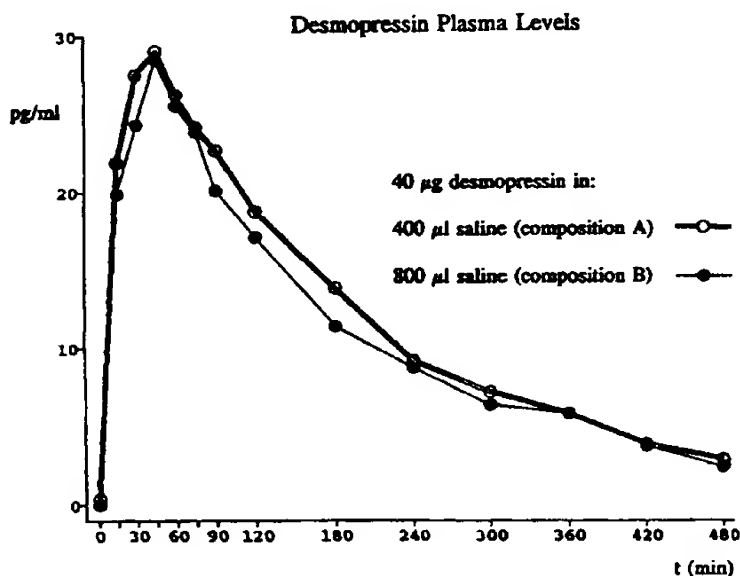
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(54) Title: COMPOSITIONS FOR NASAL ADMINISTRATION OF DESMOPRESSIN



(57) Abstract

An aqueous composition for spray nasal administration of a synthetic analog of vasopressin (desmopressin; 1-deamino-8-D-arginine-vasopressin) contains between 2.5 and 7.5 µg per 100 µl. The composition may additionally contain an osmotic-pressure controlling agent, such as sodium chloride, a preservative, such as chlorobutanol or benzalkonium chloride, and a buffer stabilizing the pH between about 4 and 6. Buffers containing citrate and/or phosphate are preferred. Also disclosed is a sealed container filled with the composition, an assembly comprising the container and a spray pump, and the use of the composition, the container, and the assembly in the management of urinary disorders.

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COMPOSITIONS FOR NASAL ADMINISTRATION OF DESMOPRESSIN.

The present invention is a composition for spray delivery to the nasal mucosa of 1-deamino-8-D-arginine-vasopressin (desmopressin).

5 Desmopressin, 1-(3-mercaptopropionic acid)-8-D-arginine-vasopressin (hereinafter also abbreviated as "DDAVP") is an analog of the neurohypophyseal peptide vasopressin. DDAVP is indicated in the management of a variety of
10 medical conditions such as irregular urination or diurea, particularly those associated with diabetes insipidus and nocturnal enuresis.

DDAVP is currently available as an aqueous nasal spray
15 composition which is administered by means of a metered spray pump. For instance, MINIRIN® nasal spray, Ferring AB, Sweden, contains 10 µg of desmopressin acetate per 100 µl, 0.5 % of chlorobutanol (w/v) as preservative, and sodium chloride. Intranasal administration of about 200 µl
20 MINIRIN® spray, containing about 20 µg of desmopressin, provides an antidiuretic effect lasting in most adult patients for about 8 to 12 hours.

In a minority of cases a dose of up to 40 µg (400 µl) is
25 required for similar effects.

For most nasally administered agents, the capacity of the human nasal cavity surface for holding aqueous solutions is limited. In most adults, this capacity is about 400 µl.
30 For efficient systemic absorption of nasally administered therapeutics, the vehicle carrying the drug must remain in contact with the mucus-lined epithelium for a sufficient period of time.

400 µl volume is close to the maximum useful volume for
35 known nasal spray compositions containing desmopressin. Nasal spray compositions having low concentrations of

DDAVP might allow coverage of a wider range of patients, such as including very young or elderly patients. However, even such dilute concentrations must be delivered in minute doses because of the potency of DDAVP. On the other hand, about 100 μ l (containing a dose of 10 μ g) of known solutions containing DDAVP is the lowest dose volume that can be conveniently reproduced by single actuations of the metered spray pump, and remain therapeutically effective.

10 Harris et al., J. Pharm. Sci. 77 (1988) 337-339, conducting experiments based on healthy human volunteers, state that a given amount of desmopressin in larger volume, when given in a single dose, is absorbed substantially less effectively than the same amount in a smaller volume (see Fig. 1, Harris, ibid.). These findings are in full agreement with those of Anik et al., J. Pharm. Sci. 73 (1984) 684-685, who conducted similar tests on rhesus monkeys with nasally administered solutions containing the decapeptide nafarelin acetate. Both reports favor higher concentrations and discourage use of more dilute solutions.

The known results obtained with desmopressin are based on analysis of plasma levels of desmopressin and factor VIII:C. The release into plasma of factor VIII:C is known to be stimulated by high doses of desmopressin. The dosage administered intranasally in such experiments was approximately 300 μ g, about ten times the average dose given to patients with urinary disorders.

30 Thus, there exists a problem in the art for achieving a balance between therapeutic needs and dosage related problems of DDAVP nasal compositions. There is a need in the art for precisely metered, easily administered, and consistently reproducible nasal delivery compositions containing DDAVP.

An object of the present invention is to provide a nasal spray composition containing desmopressin which allows effective delivery to a wider range of patients, including very young and elderly patients.

5

Another object is to provide an aqueous composition for nasal administration of between 2.5 and 7.5 μg of desmopressin per 100 μl , which allows consistent delivery of optimum therapeutic doses of the DDAVP.

10

Further objects include the provision of a sealed container for delivery of DDAVP nasal compositions, an assembly comprising the sealed container and a spray pump, and the use of the composition, the container, and the assembly in the management of urinary disorders.

15

It has now been surprisingly found that the known relationship between the concentration of desmopressin in the aqueous carrier for nasal spray administration, said concentration being a desmopressin concentration of at least 1 μg per 100 μl , and desmopressin uptake by the nasal mucosa, which relationship dissuades from using more dilute solutions, does not hold for substantially smaller desmopressin concentrations, such as concentrations ranging from 2.5 μg to 7.5 μg per 100 μl .

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In accordance with the invention, there is disclosed an aqueous nasal spray composition containing between 2.5 and 7.5 μg of desmopressin per 100 μl , the preferred concentration being about 5 μg desmopressin per 100 μl aqueous composition. It has been unexpectedly found that these optimum ranges provide ideal nasal delivery conditions for optimal therapeutic effects for desmopressin.

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A preferred embodiment of the composition according to the present invention comprises an osmotic pressure-

controlling agent, such as sodium chloride, and a preservative, such as chlorobutanol or a quaternary amine preservative such as benzalkonium chloride.

5 According to another embodiment, the composition additionally comprises a buffer, preferably a buffer comprising citrate and/or phosphate. The buffer used in the present compositions should maintain the pH from about 4 to about 6, preferably a pH of about 5.

10

It is especially preferred for the composition to comprise both benzalkonium chloride and the above-defined buffer, which makes the DDAVP nasal compositions of the present invention room-temperature stable, with shelf lives
15 exceeding one year.

15

Additionally the composition according to the invention may contain absorption enhancers such as bile salts, monolauryl ethers of macrogols, phospholipids and fusidate
20 derivatives.

20

It is preferred for the composition according to the invention to be administrable in a metered dose or multiples thereof, said metered dose comprising from 2.5
25 μg to 7.5 μg of desmopressin dissolved in from 50 μl to 150 μl of an aqueous carrier to provide a desmopressin concentration in said carrier ranging from 2.5 μg to 7.5 μg per 100 μl , for effecting a plasma profile essentially corresponding to that obtainable by single or multiple
30 dose nasal administration of the same total amount of desmopressin dissolved in said carrier in substantially higher concentration.

30

It is also preferred for the composition according to the invention to be administrable in a metered dose or
35 multiples thereof, said metered dose comprising from 2.5 μg to 7.5 μg of desmopressin dissolved in from 50 μl to

35

150 μ l of an aqueous carrier, for effecting a plasma profile essentially equivalent, on a desmopressin unit dose weight basis, to a desmopressin plasma profile obtainable by nasal administration of a metered dose of desmopressin comprising substantially higher amounts of desmopressin in a corresponding smaller volume of aqueous carrier ranging from 50 μ l to 150 μ l.

Also disclosed is a sealed container filled with an aqueous desmopressin spray composition according to the invention and its use in connection with a spray pump. The container and the pump may be integrated as a unit and can also be made disposable. It is preferred for the pump to be a metered precompression spray pump. The pump is preferably designed for delivering a dose ranging from 2.5 to 7.5 μ g desmopressin per actuation, with the optimum amount at about 5 μ g.

The composition according to the invention is used for effective therapeutic management of various urinary disorders, such as diabetes insipidus, incontinence, and enuresis, particularly nocturnal enuresis.

FIGURE 1 graphically depicts therapeutical bioequivalence of known DDAVP nasal solutions and the DDAVP aqueous nasal compositions of the present invention.

The invention will now be explained in detail by reference to the following experimental examples.

30

EXAMPLE 1

Preparation of test solutions. Two desmopressin acetate nasal spray compositions (A and B) were prepared under aseptic conditions by dissolving the following components in 1 l of Millipore®-filtered water:

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composition	A	B
desmopressin acetate	100 mg	50 mg
chlorobutanol*	5 g	5 g
5 sodium chloride	9 g	9 g

* 1,1,1-trichloro-2-methylpropan-2-ol

10 pH was adjusted to 3.5 - 5.0 by addition of 2 N HCl. A denotes a currently known composition which was prepared for comparison, while B denotes the composition made according to the present invention.

EXAMPLE 2

15

Comparative testing. 24 healthy male volunteers were given 40 μ g of desmopressin in the form of composition A from Example 1 (administration of a 4 x 100 μ l = 400 μ l dose). After an interval of at least one week, the same test
20 subjects were given desmopressin in the form of composition B (administration of a 8 x 100 μ l = 800 μ l dose). Commercially available, metered-dose spray pumps manufactured by Erich Pfeiffer AG, Rudolfzell, Germany, set to the appropriate dosage volumes were used.

25

Blood was collected by venipuncture before administration (control) and at times 5, 15, 30, 45, 60, and 90 minutes, and 2, 4, 6, and 8 hours after administration. Plasma desmopressin was assayed by RIA as described by Harris, et
30 al., J. Pharm. Sci. 77 (1988) 337-338 (for statistical treatment of data, see Harris ibid., p. 338).

The results are graphically depicted in Fig. 1, which shows plasma levels of desmopressin as a function of time.
35 It is evident from Fig. 1 that composition (A) and the composition according to the present invention (B) are bioequivalent and therefore therapeutically equivalent. It

can also be seen that composition (B) has a substantially broader useful administration range.

EXAMPLE 3

5

Long shelf-life composition. A nasal spray composition according to the present invention having a shelf life of more than one year at room temperature was prepared by dissolving in 1000 ml of Millipore®-filtered water: 50 mg
10 of desmopressin acetate, 1.0 g of benzalkonium chloride, 6.3 g of sodium chloride, 1.56 g of citric acid, and 2.43 g of disodium hydrogen phosphate.

While the various embodiments of the present invention
15 have been described herein, it is possible that one skilled in the art could modify the various reagents and reaction conditions and obtain similar results. Such modifications are contemplated as being within the scope of the present disclosure.

20

C l a i m s

- 5 1. An aqueous composition for nasal administration of desmopressin, comprising between about 2.5 and about 7.5 μg desmopressin per 100 μl of said aqueous composition.
- 10 2. The composition according to claim 1, wherein said composition contains about 5 μg desmopressin per 100 μl .
3. The composition according to claim 1, further comprising an osmotic pressure-controlling agent.
- 15 4. The composition according to claim 3, wherein said osmotic pressure-controlling agent is sodium chloride.
5. The composition according to claim 1, further comprising a preservative.
- 20 6. The composition according to claim 5, wherein said preservative is chlorobutanol.
7. The composition according to claim 5, wherein said
- 25 7. preservative is a quaternary amine.
8. The composition according to claim 7, wherein said quaternary amine is benzalkonium chloride.
- 30 9. The composition according to claim 1, further comprising a buffer.
10. The composition according to claim 9, wherein said buffer comprises citrate and/or phosphate.
- 35 11. The composition according to claim 10, wherein said buffer maintains a pH from about 4 to about 6.

12. The composition according to claim 11, wherein said buffer maintains pH at about 5.

13. The composition according to claim 1, further
5 comprising at least one absorption enhancing agent.

14. The composition of claim 13, wherein said absorption enhancing agent is selected from the group consisting of bile salts, monolauryl ethers of macrogols,
10 phospholipids, and fusidate derivatives.

15. The composition according to claim 1, administrable in a metered dose or multiples thereof, said metered dose comprising from 2.5 μg to 7.5 μg of desmopressin dissolved
15 in from 50 μl to 150 μl of an aqueous carrier to provide a desmopressin concentration in said carrier ranging from 2.5 μg to 7.5 μg per 100 μl , for effecting a plasma profile essentially corresponding to that obtainable by nasal administration of the same total amount of
20 desmopressin dissolved in said carrier in substantially higher concentration.

16. The composition according to claim 1, administrable in a metered dose comprising from 2.5 μg to
25 7.5 μg of desmopressin dissolved in from 50 μl to 150 μl of an aqueous carrier, for effecting a plasma profile essentially equivalent, on a desmopressin unit dose weight basis, to a desmopressin plasma profile obtainable by nasal administration of a metered dose of desmopressin
30 comprising substantially higher amounts of desmopressin in a corresponding smaller volume of aqueous carrier ranging from 50 μl to 150 μl .

17. An aqueous composition for nasal administration of
35 desmopressin, comprising:

a) between about 2.5 and about 7.5 μg desmopressin per

100 μ l;

- b) benzalkonium chloride;
- c) an absorption enhancing agent selected from the group consisting of bile salts, monolauryl ethers of
5 macrogols, phospholipids, and fusidate derivatives;
 and
- d) a buffer comprising phosphate and citrate, such that
 said buffer has substantial buffering capacity at a
 pH from 4 to 6.

10

18. A sealed container containing an aqueous
desmopressin spray composition according to claim 16.

15

19. An assembly comprising a sealed container according
to claim 18 and a precompression spray pump.

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20. The assembly according to claim 19, wherein said
spray pump delivers a dose volume containing from about
2.5 μ g to about 7.5 μ g desmopressin per actuation.

21. The assembly according to claim 20, wherein said
dose volume contains about 5.0 μ g desmopressin per
actuation.

25

22. A method for treating urinary disorders with the
composition according to claim 1.

30

23. The method of claim 22, wherein said disorder is
selected from the group consisting of diabetes insipidus,
incontinence, enuresis and nocturnal enuresis.

24. A method for treating urinary disorders with the
composition according to claim 17.

35

25. The method of claim 24, wherein said disorder is
selected from the group consisting of diabetes insipidus,
incontinence, enuresis and nocturnal enuresis.

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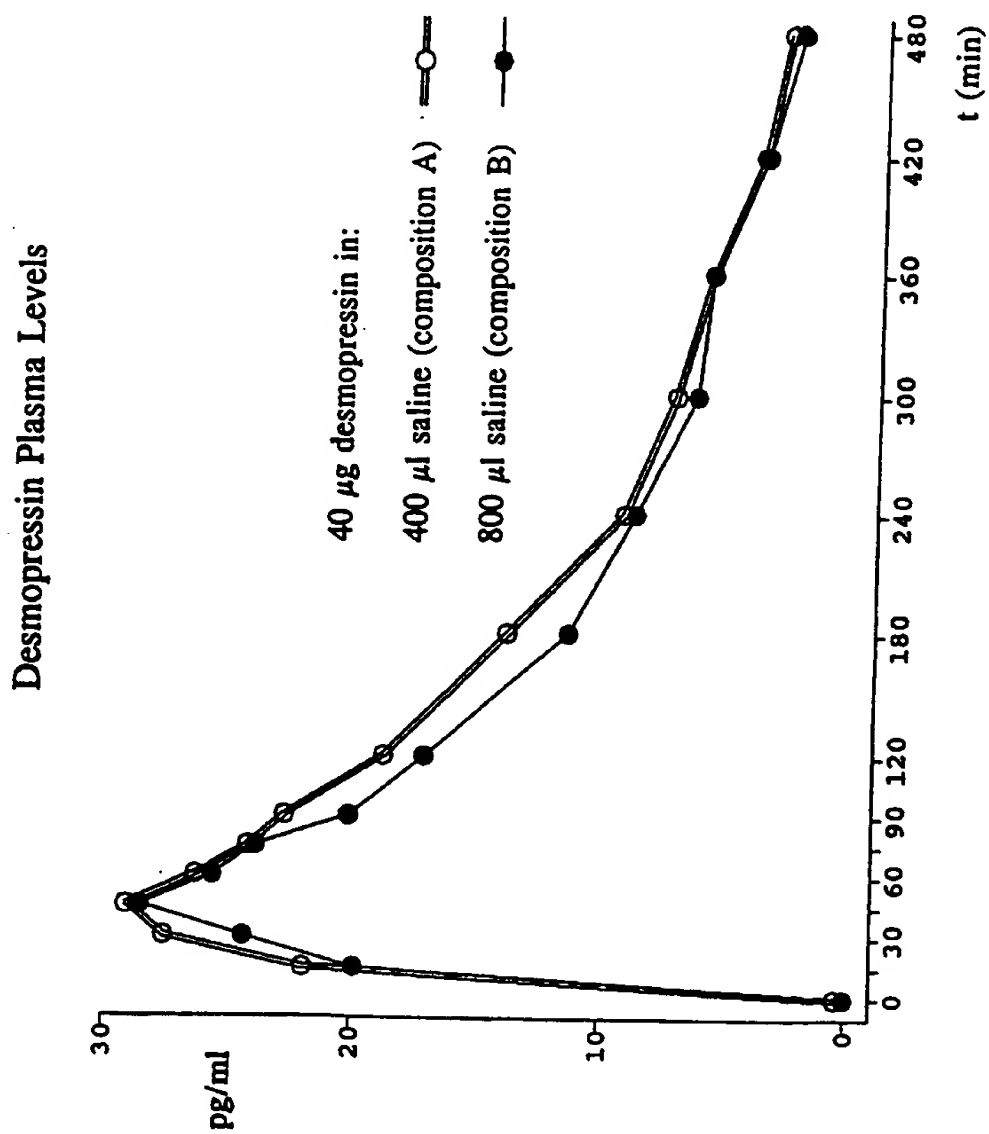


Fig. 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00623

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 37/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, EMBASE, WPI, CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A1, 0381345 (CORINT, LTD.), 8 August 1990 (08.08.90) --	1-21
A	WO, A1, 8805661 (BIOMED RESEARCH CONSULTANTS LIMITED), 11 August 1988 (11.08.88) --	1-21
A	The Lancet, 1968, I Vavra et al: "Effect of a Synthetic Analogue of Vasopressin in Animals and in Patients with Diabetes Insipidus", see page 948 - page 952 -- -----	1-21

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

5 October 1994

Date of mailing of the international search report

12 -10- 1994

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00623

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 22-25
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1 (iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/08/94

International application No.

PCT/SE 94/00623

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0381345	08/08/90	AT-T- 108326 DE-D- 69010518	15/07/94 00/00/00
WO-A1- 8805661	11/08/88	EP-A- 0300036	25/01/89